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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/532,563

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Jan-Henrik Ardenkjaer-Larsen

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EXAMINER

SCHLIENTZ, LEAH H

ART UNIT

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1618

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/532,563	Applicant(s) ARDENKJAER-LARSEN ET AL.	
	Examiner Leah Schlientz	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 September 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-9 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 9/7/2010, in reply to the Office Action mailed 5/7/2010, is acknowledged and has been entered. Claims 1 and 9 have been amended. Claims 1 and 3-9 are pending and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments filed 9/7/2010 have been fully considered but they are not persuasive, for reasons set forth hereinbelow.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method for producing hyperpolarized ^{129}Xe comprising a) preparing a mixture of xenon, at least one solvent or a mixture of solvents which is a single chain alcohol or a glycol having good glass-forming properties and/or has lipophilic properties, and a free radical, b) hyperpolarizing said mixture according to the DNP method to obtain hyperpolarized ^{129}Xe and c)

Art Unit: 1618

optionally separating said xenon from the other components of the mixture. The claims are confusing because there are at least two reasonable interpretations regarding the identity of the solvent. For example, based on the and/or language in line 3 of the claim, one interpretation of the claims could be "a solvent or mixture of solvents which is a single chain alcohol or a glycol having good glass-forming properties and has lipophilic properties," or another interpretation of the claims could read "a solvent or mixture of solvents which has lipophilic properties." Therefore, the identity of the nature of the solvent is unclear and as such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained. It is unclear if the second recitation of "has lipophilic properties" is related to the "single-chain alcohol or a glycol" or if this limitation stands alone.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

Art Unit: 1618

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 3-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ardenkjaer-Larsen *et al.* (US 6,466,814) in view of Pines (US 6,426,058).

Ardenkjaer-Larsen teaches hyperpolarization of a nuclei effected by a hyperpolarizable gas, such as by (a) hyperpolarizing a hyperpolarizable gas before, during or after introducing a high T_1 agent thereto whereby to cause nuclear polarization of said high T_1 agent; and b) dissolving in a physiologically tolerable solvent said high T_1 agent (column 19, lines 1-12). Physiologically tolerable solvent includes perfluorocarbon (column 3, line 8). Hyperpolarizable gas is preferably ^{129}Xe (column 19, line 28). It can be produced by irradiating agent e.g. with an electron spin resonance transition stimulating radiation (e.g. microwave radiation). For example, hyperpolarization of xenon can be accomplished by irradiating a polarizing agent whereby to cause dynamic nuclear polarization; polarizing agents include nitroxide, trityl, etcl (radicals) (column 19, lines 63 - column 20, line 9). Hyperpolarization could be done in either liquid or solid form, the radical could be added in pure form or bound to a matrix. After irradiation, heating of the sample could release hyperpolarized gas and a new batch of xenon could be condensed and irradiated (column 20, lines 10-30).

While Ardenkjaer-Larsen discloses a) hyperpolarising a hyperpolarisable gas before, during or after introducing a high T_1 agent thereto and b) dissolving in a physiologically tolerable solvent (e.g. perfluorocarbon) said high T_1 agent, rather than introduction of solvent prior to hyperpolarization of the hyperpolarisable gas, it would

Art Unit: 1618

have been obvious to one of ordinary skill in the art at the time of the invention to modify the order of addition of solvent in the process of Ardenkjaer-Larsen.

Pines teaches methods in which hyperpolarized noble gases (e.g., Xe and He) are used to enhance and improve NMR and MRI (abstract). Two methods known in the art for enhancing the spin polarization of a population of nuclei are dynamic nuclear polarization and optical pumping (column 2, lines 35+). It is desirable to predissolve the hyperpolarized noble gas in a fluid which can, for example, prolong its relaxation time when the hyperpolarized xenon is in contact with physiological fluids. For instance, if the hyperpolarized gas is to be injected into blood, it is desirable to first pre-dissolve the hyperpolarized gas in a lipid, lipid solution or lipid emulsion to form a mixture which, in turn, is injected into the blood. Also desirable is dissolving the hyperpolarized noble gas in a fluorocarbon, fluorobon solution or fluorocarbon emulsion (column 9, line 5-20). It can be advantageous to dissolve a noble gas in a liquid prior to hyperpolarizing the noble gas (column 9, lines 25-30). Preferred noble gases include xenon, helium, etc. (column 9, lines 5-10). Suitable liquids/fluids include fluorocarbons, lipids, ethanol, etc (column 9-10).

It would have been obvious to one of ordinary skill in the art at the time of the invention to dissolve xenon in a fluid such as perfluorocarbon prior to hyperpolarizing the xenon in the methods of Ardenkjaer-Larson. One would have been motivated to do so because Pines teaches that it can be advantageous to dissolve a noble gas in a liquid prior to hyperpolarizing the noble gas (column 9). One would have had a reasonable expectation of success in doing so because Ardenkjaer-Larson teaches that

Art Unit: 1618

hyperpolarization could be done in either liquid or solid form, the radical could be added in pure form or bound to a matrix (column 20).

Response to Argument

Applicant argues on pages 4-6 of the Response that the present invention is directed to a new and improved method for producing hyperpolarized ^{129}Xe . A high level of polarization is obtained by this method. As stated in the description and illustrated in the Examples, the presence of the solvent or solvent mixture prior to hyperpolarisation dramatically increases polarization enhancement (comparison Examples 1 and 2 versus Examples 3-10). Claims 1 and 9 have been amended to a method including the use of preferred solvents, in line with the Examples. Applicant further argues that as xenon is a rather lipophilic compound the applicant has found that it is favourable to use a lipophilic solvent to properly dissolve Xe in the solvent, and that applicant has found that both when the solvent(s) are included, and which type of solvent(s) are used, are critical to achieve such high levels of polarization.

This is not found to be persuasive. As set forth above, the identity of the solvent in the claims is unclear, which may be directed to an alcohol or glycol having good glass-forming properties and/or lipophilic properties; or may be interpreted to read on a solvent which has lipophilic properties. It is considered that the perfluorocarbons listed in Ardenkjaer-Larson and Pines are readable upon a solvent which has lipophilic properties. In addition, Pines teaches ethanol as a suitable liquid/fluid carrier, and teaches that it may be desirable to dissolve a noble gas in a liquid prior to hyperpolarizing (column 9). Regarding the data provided in Examples 1-10, it is noted

Art Unit: 1618

that the data are directed to a few example solvents, while the claims are readable upon a range of solvents, such as an alcohol or glycol having good glass-forming properties and/or lipophilic properties; or may be interpreted to read on a solvent which has lipophilic properties. Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980). See MPEP 716.02(d).

Applicant argues that Ardenkjaer-Larsen discloses a method of MR investigation including producing a hyperpolarized solution of a high T1 agent. A solid sample of the T1 agent is hyperpolarized and then dissolved in a physiologically tolerable solvent. Further, the applicant disagrees that it would be obvious to modify the order of the addition of the solvent in the process of Ardenkjaer-Larsen, as the purpose and the function of using the solvent is different for the two inventions. Ardenkjaer-Larsen uses the solvent simply to dissolve the hyperpolarized solid sample before administration to a body. However, in the present invention the solvent is used as an additive in the DNP hyperpolarization of xenon and this dramatically increases polarization enhancement. Hence, there is no motivation by Ardenkjaer-Larsen to modify the order of addition of solvent in the process of Ardenkjaer-Larsen. Pines provides methods for using hyperpolarized noble gases in conjunction with NMR spectroscopy and MRI, and suggests a method for analyzing a sample wherein a noble gas is combined

Art Unit: 1618

with a fluid to form a mixture that can be delivered to blood or other tissue while the noble gas still has a large off-equilibrium nuclear spin polarization. A long list of fluids is suggested, focusing on fluorocarbons. Pines states that it is preferable to dissolve the hyperpolarized gas in a fluid that can prolong its relaxation time. Hence, the purpose of the fluid (solvent) of Pines is for administration purposes and for prolonging of the relaxation time. In the entire disclosure, Pines provides only a single sentence indicating that it can be advantageous to dissolve the noble gas in a liquid prior to hyperpolarizing the noble gas, furthermore there is no teaching as to why this should be done. Hence, in view of all of the other teachings and details in Pines, the skilled man reading Ardenkjaer-Larsen seeking an improved method for hyperpolarizing xenon would not find any guidance for modifying Ardenkjaer-Larsen so as to arrive at the invention as presently claimed.

This is not found to be persuasive. In response to applicant's argument that in the present invention the solvent is used as an additive in the DNP hyperpolarization of xenon and this dramatically increases polarization enhancement, it is respectfully submitted that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). See MPEP 2144 IV. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by

Art Unit: 1618

applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). In the instant case, Pines specifically teaches that when dissolving hyperpolarized in a fluid (including various perfluorocarbons, ethanol, etc. as liquid/fluid) gas can prolong its relaxation time, teaches that it can be advantageous to dissolve a noble gas in a liquid prior to hyperpolarizing the noble gas.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1618

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS